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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,672	03/08/2002	Mingdong Zhou	524012000200	6586

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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,672	ZHOU, MINGDONG	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1,3-15,18-24,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6-17 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *In part* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept.

In accordance with 37 CFR 1.142, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1, and 3-5, drawn to a method of causing cardiomyocyte growth and/or differentiation using neuregulin (NRG), classified in class 514, subclass 2.

II. Claims 2, 16-17, and 25-29, drawn to a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions using NRG (or its derivatives), causing cardiomyocyte growth and/or differentiation, classified in class 514, subclass 2 (different process/search than Group I).

III. Claims 6-12, drawn to a method of identifying polypeptides or compounds which stimulate cardiac muscle cell differentiation using NRG and a test polypeptide or compound, classified in class 424, subclass 9.34.

IV. Claims 13-15, drawn to a method of identifying polypeptides or compounds which inhibit NRG stimulation of ventricular muscle cell differentiation, using a test polypeptide or compound, classified in class 424, subclass 9.34 (different process/search than Group III)

V. Claim 18, drawn to a method of preventing or lowering the incidence of heart disease in a mammal, comprising preventing or lowering the interference or

effects of polypeptides or compounds on the action of NRG and its receptors, ErbBs, that produces heart failure, classified in class 424, subclass 1.69.

VI. Claim 19, drawn to a compound ("use of" unclear) that mimics the effects of neuregulin to treat or prevent PE, or IGF-1-mediated cardiac muscle cell dysfunction, classified in class 530, subclass 300+.

VII. Claims 20-21, drawn to a method of determining predisposition to heart disease or heart failure in a subject, comprising testing cardiac or related muscle cells of the subject for the ability to express and/or produce normal or adequate levels of neuregulin or its cognate ErbB receptors, classified in class 435, subclass 7.8.

VIII. Claims 22-23, drawn to a compound ("use of" unclear) of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the treatment or management of heart disease and heart failure in a mammal, classified in class 530, subclass 300+.

IX. Claim 24, drawn to a compound ("use of" unclear) of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the manufacture of a medicament for the treatment or management of heart disease and heart failure, classified in class 530, subclass 300+.

The inventions are distinct, each from the other because of the following reasons:

The methods (and/or compounds) in Groups I-IX are directed to different inventions, which are not connected in design, operation, and/or effect. These methods are independent since they are not disclosed as capable of use together, they have different modes of operation,

they have different functions, and/or they have different effects. One would not have to practice the various methods at the same time to practice just one method alone.

The several inventions (Groups I-IX) above are independent and distinct, each from the other. They have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference, which would anticipate the invention of one group, would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application. Restriction for examination purposes is therefore proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CRF 1.143).

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Peng Chen on 9/15/03, a provisional election was made with traverse to prosecute the invention of Group II, claims 2, 16-17, and 25-27. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1, 3-15, 18-24, 28 and 29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating and/or reducing the risk of dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures, via administering neuregulin, does not reasonably provide enablement for preventing dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures using neuregulin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants have reasonably demonstrated/disclosed that the claimed neuregulin is useful as a therapeutic agent for treating dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures and/or reducing the risk thereof. However, the claims also encompass using the claimed neuregulin to prevent dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" is an absolute

definition which means to stop from occurring and, thus, requires a higher standard for enablement than does the term "treat", especially with respect to preventing type II diabetes (which, is not recognized in the medical art as being a totally preventable condition).

Accordingly, it would take undue experimentation without a reasonable expectation of success for one of skill in the art to make and/or use the claimed composition which would function to prevent dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 16, it is unclear what is contemplated by "neuregulin or its derivatives"? Namely, the claims/specification do not define 'what' neuregulin compound (structure or sequence) is to be used in the invention. Further, the claims/specification do not describe what all the possible derivatives of neuregulin are. Thus, without a clear definition of what neuregulin compound is to be used (assuming that the structure and function of distinct neuregulin compounds may be different), it is not understood what "neuregulin or its derivatives" encompasses, as contemplated for use in the invention. It is suggested that Applicant distinctly

claim the subject matter of neuregulin by structure or sequence, including any derivatives contemplated for use in the invention.

In claim 16, it is unclear what a "therapeutically effective amount" is? Neuregulin is a known cardiac muscle cell chemical with known activation mechanisms (see below); however, what constitutes the "therapeutically effective amount" to carry out the level of remodeling or treatment (or prevention) or improvement of normal or diseased heart, is unclear. It was not found in the specification where this was tested and proven, defined, or described. Applicant is asked to point out where in the specification such may be found, or distinctly claim the subject matter of what constitutes a "therapeutically effective amount" (within the confines of may be supported by "Written Description").

In claim 25, it is unclear what genes are contemplated within the phrase "inducing expression of the gene(s) involved in neuregulin production"? It was not found in the specification what genes are involved in such production or capable of producing such production "in other cells"? Since it cannot be assumed what these genes are, or that all genes capable of producing neuregulin will stimulate the types of neuregulin (see above on the issue of which "neuregulins" may be used in the invention) capable of inducing/treating (preventing)/improving the conditions targeted by the method of use claimed. Applicant is asked to point out where in the specification these "genes" are defined/described. Where such support may be found, it is suggested that Applicant distinctly claim these genes.

In claim 26, it is unclear what cells, in the phrase "produced by some other cell", are capable of producing neuregulin, in a paracrine manner? Although the art teaches that compounds such as neuregulin may be biologically stimulated for release in an autocrine or

paracrine manner generally; Applicant has specifically claimed that the present method may be carried out by causing neuregulin to be produced by other cells. In order for the method to be carried out, one of skill in the art would need to be apprised of which "other cell(s)" need to be stimulated and how. Applicant has claimed neither "which cell(s)" are to be stimulated or active steps which show that the appropriate "other cell(s)" are targeted and produce neuregulin (or what compounds, or otherwise, are capable of stimulating "other cell(s)" in order to then produce neuregulin). Such descriptions/definitions were not found in the specification. Therefore, it is unclear how the method can be practiced and a competitor would not be apprised as to whether he may be infringing the present method invention. Applicant is asked to point out where in the specification these "other cell(s)" are defined/described. Where such support may be found, it is suggested that Applicant distinctly claim these "other cell(s)" or active steps leading to stimulating "other cell(s)" in order to then produce neuregulin.

In claim 27, it is unclear what is contemplated by the term "improved"? Namely, what range or degree of improvement of a normal or diseased heart (including what types of heart conditions, since cannot be assumed that use of neuregulin can "improve" any normal or diseased heart)? Such a description or definition was not found in the specification. It is suggested that Applicant distinctly claim what degree of improvement has been tested and proven, as to a normal heart, as well as to what heart diseases, use of neuregulin was found to render improvement, including what degree of improvement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claimed invention is drawn to a method of inducing inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions, comprising the treating cardiac muscle cells with neuregulin (thereby activating the MAP kinase pathway in the cells and causing remodeling of the cell structures or the cell-cell adhesions) (claim 2); or treating (or preventing) disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures, comprising administering a therapeutically effective amount of neuregulin or its derivatives (claim 16); directed to treating heart failure resulting from cardiac muscle cell-cell adhesion and/or the disarray of sarcomeic structures (claim 17); wherein neuregulin is provided directly to the cardiac cell (autocrine manner or produced by some other cell and

released in a paracrine manner (claim 26)) or provided indirectly by causing neuregulin to be produced in other cells by inducing expression of the gene(s) involved in neuregulin production (claim 25); wherein a normal or diseased heart is improved by treatment with neuregulin (claim 27).

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/26298 (Cambridge Neuroscience; Sklar et al.).

WO 94/26298 teach the use of neuregulin (and other related compounds/mimics), by contacting muscle cells (p. 3, lines 30-31), and specifically cardiac muscle cells (abstract; p. 3, line 17) and namely "any cell which contributes to muscle tissue" (p. 4, lines 17-18), in methods for normal and diseased hearts (p. 8-9) for "muscle regeneration" (p. 2, col. 12) in order to induce "both the proliferation of muscle cells and the differentiation and survival of myotubes" (p. 3, lines 15-17) and "the mitogenesis, survival, growth and differentiation of muscle cells" (p. 3, col. 26-29); wherein "[m]yogenesis . . . refers to any fusion of myoblasts to yield myotubes" [i.e. remodeling and increased cell-cell adhesion]. WO 94/26298 further teach that administration if to a vertebrate, preferably a mammal (p. 4, line 5) and that "[n]euregulin effects on muscle may occur, for example, by inducing the synthesis of particular isoforms of the contractile apparatus such as the myosin heavy chain slow and fast isoforms; by promoting muscle fiber survival via the induction of synthesis of protective molecules such as, but not limited to, dystrophin; and/or by increasing acetylcholine receptor molecules at the neuromuscular junction (p. 4, lines 7-16) (see also claims, including nucleic acid (gene) stimulation).

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Sklar et al. (US 644642 B1; Cambridge Neuroscience).

Sklar et al., also assigned to Cambridge Neuroscience, teach the same invention elements discussed above in WO 94/26298 (see claims 1-40).

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Gwynne et al. (US 6087323; Cambridge Neuroscience).

Gwynne et al., also assigned to Cambridge Neuroscience, teach the same invention elements discussed above in Sklar et al. and WO 94/26298 (see claims 1-40).

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 99/18976 (Cambridge Neuroscience; McBurney et al.).

WO 99/18976, also assigned to Cambridge Neuroscience, teach the same invention elements discussed above in Sklar et al., WO 94/26298, and Gwynne et al. (see claims 1-36).

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Balligand et al. (Jan./Feb.), 1997; 3(4):351-360).

Balligand et al. teach the use of neuregulin, as a paracrine/autocrine acting trophic factor, synthesized and released by cardiac myocytes and/or endothelial cells (p. 351, 1st ¶); in cardiac endothelium and tissue growth, and specifically regulation of cardiac myocyte growth (in the

developed myocardium; page 354, 2nd ¶) as well as vasculogenesis and angiogenesis, and in the function of cardiac muscle following development (abstract);

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of WO 94/26298 (Cambridge Neuroscience; Sklar et al.), Sklar et al. (US 644642 B1; Cambridge Neuroscience), Gwynne et al. (US 6087323; Cambridge Neuroscience), WO 99/18976 (Cambridge Neuroscience; McBurney et al.), or Balligand et al. (Jan./Feb.), 1997; 3(4):351-360).

The five references are all discussed above.

Applicant's claims do not expressly teach that the neuregulin is in any composition or pharmaceutical composition for use in the method of treatment; however, even if such were claimed, and not expressly taught by the references above, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a neuregulin composition/pharmaceutical composition (*even with other components*); because all the references teach that neuregulin is a known natural compound released within cardiac muscle tissue and known to function biologically, in an apocrine or paracrine manner by activation of the MAP kinase pathway in the cells, to induce remodeling of cardiac muscle cell sarcomeric and

cytoskeleton structures, or cell-cell adhesions, in normal or diseased hearts (or lacking thereof in the latter); or to treat disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
September 30, 2003

CHRISTOPHER R. TATE
PRIMARY EXAMINER